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## CLINICAL PRACTICE ARTICLE

**REVISED** Massive ear keloids: Natural history, evaluation of risk factors and recommendation for preventive measures – A retrospective case series [version 2; referees: 1 approved, 2 approved with reservations]

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**Abstract**

Keloid disorder (KD) is an inherited wound healing ailment, frequently seen among Africans /African Americans and Asians. Genetics of this disorder continues to be obscure and poorly understood. Clinical manifestation of KD is quite variable and very diverse, spanning from individuals with one or very few small keloidal lesions, to those with numerous and very large lesions covering large portion of their skin. Ears are common locations for development of keloids. Ear piercing is by far the leading triggering factor for ear keloid formation in genetically predisposed individuals. Although there are numerous publications about ear and earlobe keloids, there is a void in medical literature about massive ear keloids. This paper focuses on the natural history of massive ear keloids and risk factors that lead to formation of these life-changing and debilitating tumors and recommendations for prevention.

**Open Peer Review**

Referee Status: ? ✓ ?

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	1	2	3
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**REVISED Amendments from Version 1**

Changes made to V2 were made based on the comments made by the reviewers. These changes included re-organizing sections of the manuscript, and adding further statistical analysis. This resulted in 2 new figures and 2 new tables being added to describe the statistics. Furthermore, 3 new references have been added.

**See referee reports**

## Introduction

Patients with keloid disorder (KD) carry a genetic abnormality that predisposes them to the disorder<sup>1</sup>. Although no convincing genetic abnormalities have been linked to KD, clinical observation suggests that the genetic predisposition to KD has a broad spectrum<sup>2</sup>. Individuals who suffer from mild form of the disorder typically develop one or few slow-growing keloidal lesions, whereas individuals with the severe form of the disorder often develop several large keloids. Perhaps the strongest link to the genetic underpinning of KD is

observed in patients with Rubinstein-Taybi Syndrome, whereby a significant percentage of these patients develop keloidal skin lesions<sup>3</sup>.

In addition to the genetics, other factors also play important roles in clinical presentation of KD. Most importantly, there must exist an injury to the skin that would trigger abnormal wound healing response that leads to the formation of keloid lesions<sup>2</sup>. **Figure 1** depicts a young African American male who developed an earlobe keloid following the piercing of his right ear. In addition, he also sustained several sharp and deep injuries to his neck, left shoulder and left arm. All wounded areas subsequently transformed into linear keloids. Therefore, it is safe to conclude that had he not pierced his ear or sustained other injuries, he would not have developed any of these keloids and would have remained completely asymptomatic. Therefore, simple clinical observations of this one patient teaches us that certain individuals harbor the KD genetic abnormality yet remain asymptomatic only because they have not pierced their ears or sustained a serious injury to their skin.

Another important fact about KD, which is well exemplified in this case, is that adjacent and even distant skin are also affected by the



**Figure 1.** Young African American male with several keloidal skin lesions on various parts of his skin. Notice that each wounded area of skin has transformed into a keloidal lesion.

keloidal process; thus, the wounding of normal-appearing skin will inevitably lead to the formation of new keloid lesions.

In addition to genetics and skin injuries, the third important factor in the clinical presentation of KD is the age of the individual. The peak age of onset of KD occurs during puberty; however, certain types of skin injuries only occur later in life. For instance, the typical age of those undergoing cardiac bypass surgery or facelift surgery is in 6th and 7th decade of life. As such, certain KD carriers will remain asymptomatic until they undergo their first surgery and end up with chest-wall or peri-auricular keloids<sup>1,4</sup>. Race, gender, passage of time and therapeutic interventions are other important factors that play their own unique roles in clinical presentation of this disorder. The wide spectrum of these factors contributes to highly variable phenotype of KD. The clinical presentation of KD is to some extent race and gender dependent. Large and tumoral keloids, including massive ear lesions, are more often encountered among Africans, African Americans and individuals with black skin<sup>2</sup>.

Focusing our attention to the ears, it is common knowledge that keloid lesions grow over time. With medical interventions, some KD lesions respond well to the treatments, but some lesions fail to respond, or even get worse and grow much larger. By far, the most important factor in development of all primary keloidal lesions is the initial wounding injury of the skin. However, the surgical removal of ear keloids that is commonly performed by ENT specialists, plastic surgeons and general dermatologists, defies this very basic principal of keloid formation. The extent of the injury to the surrounding skin when an ear keloid is surgically removed is obviously several fold greater than the primary injury sustained from the piercing procedure. This iatrogenic injury will undoubtedly trigger a keloidal wound healing response that is not only more intense than the one triggered by the original piercing event but also much greater in magnitude and distribution. Studies have indicated that almost all ear keloids and almost all other keloid lesions will relapse after surgery; hence, the need for adjuvant treatment has been emphasized by almost every author who has published on this topic. Adjuvant treatments in the form of post-operative steroid injections<sup>5</sup>, pressure devices<sup>6</sup> or even radiation therapy<sup>7,8</sup> are often incorporated in management of ear keloids in order to counteract the fully expected keloid recurrence after surgery. However, despite the meticulous use of all available adjuvant treatments, a large number of patients will suffer from recurrent ear keloids and undergo second, third or fourth surgeries. Unfortunately, the ear keloids will continue to relapse in many instances. At some point, the surgeon, the patient, or even both will abandon therapeutic interventions.

This article focuses on these unfortunate cases; instances of recurrent large, semi-massive, and massive ear keloids among mostly young patients who ultimately accept the reality that surgery and/or adjuvant radiation therapy cannot treat their keloids,

thereby resigning themselves to living with huge tumoral keloids hanging from their ears, an unwanted and unpleasant outcome that impacts every aspect of their daily lives.

## Materials and methods

This is a retrospective analysis of 283 consecutive patients with ear keloids who were seen by the author in his keloid specialty medical practice. Patients with post-otoplasty ear keloids (n=14), and those with post-facelift peri-auricular keloids were not included in this study as the triggering factor for these keloids, i.e. primary surgery, clearly results in a much larger injury to the ear tissue as compared to the injury from ear piercing. Author intends to publish and report these patients in a separate manuscript.

Data was analyzed using descriptive statistics. Number of patients and percentages were computed for each category. To test the differences in each dataset category, general z-test were computed. The 95% confidence intervals for the observed proportions were calculated by Clopper-Pearson method. Statistical analysis was performed using MedCalc 15.8.

The underlying research project for this retrospective study was determined by the Western IRB to meet the conditions for exemption under 45 CFR 46.101(b)(4). Consent is not required for studies that are determined to be exempt under 45 CFR 46.101(b)(4).

## Results

Keloids were assessed visually and categorized according to their size into four separate groups.

- 1- Massive ear keloids:** the size of the keloid mass is greater than the surface area of the corresponding ear. Thirteen patients (4.6%) met this criterion. Three patient were Caucasians, and 10 were African Americans. Four patients (three females and one male) had bilateral massive ear keloids. [Figure 2](#) depicts several patients in this category.
- 2- Semi-massive ear keloids:** the size of the keloid mass is at least 50% of the surface area of the corresponding ear, but smaller than massive ear keloids. Eighteen patients (6.4%) met this criterion. Two patients were Caucasians, and sixteen were African Americans. [Figure 3](#) depicts several patients in this category.
- 3- Large ear keloids:** the size of the keloid mass was more than the size of the corresponding earlobe, but smaller than semi-massive ear keloids. In total, 181 patients (64%) met this criterion. Forty-nine patients were Caucasians or Asians, and 132 patients were African Americans. [Figure 4](#) depicts several patients in this category.





**Figure 2.** Massive ear keloids are larger than the size of corresponding ear. Yellow radiation signs identify patients who have previously received adjuvant radiation therapy after removal of their ear keloids.





**Figure 3.** Semi-massive ear keloids measure at least half the size of the corresponding ear.





**Figure 4.** Large ear keloids measure larger than the corresponding earlobe.





**Figure 5.** Early stage, primary ear keloids in various stages of development.

**4- Small ear keloids:** the size of the keloid mass is less than the size of the corresponding earlobe. Seventy-one patients (25%) met this criterion. Twenty-eight patients were Caucasians or Asians, and 43 patients were African Americans. [Figure 5](#) depicts several patients in this category.

[Table 1](#) summarizes characteristics of the patients within each group.

Other than author's recently published keloid staging system<sup>8</sup>, there are no other previously described methodologies that would allow for more precise grouping of the ear keloids. [Table 2](#) shows the stage classification of solitary ear keloids according to the this staging system.

Proportionally, more females were noted among each study group ([Figure 6](#)), however, this finding may simply be related to the fact that more women pierce their ears. The proportional difference between females and males is statistically significant and shown in [Table 3](#) (95% CI of observed proportion for female gender is 55.05%-66.72%,  $Z=3.701$ ,  $P=0.0002$ ).

Proportionally, there were more Africans/African Americans among each study group ([Figure 7](#)).

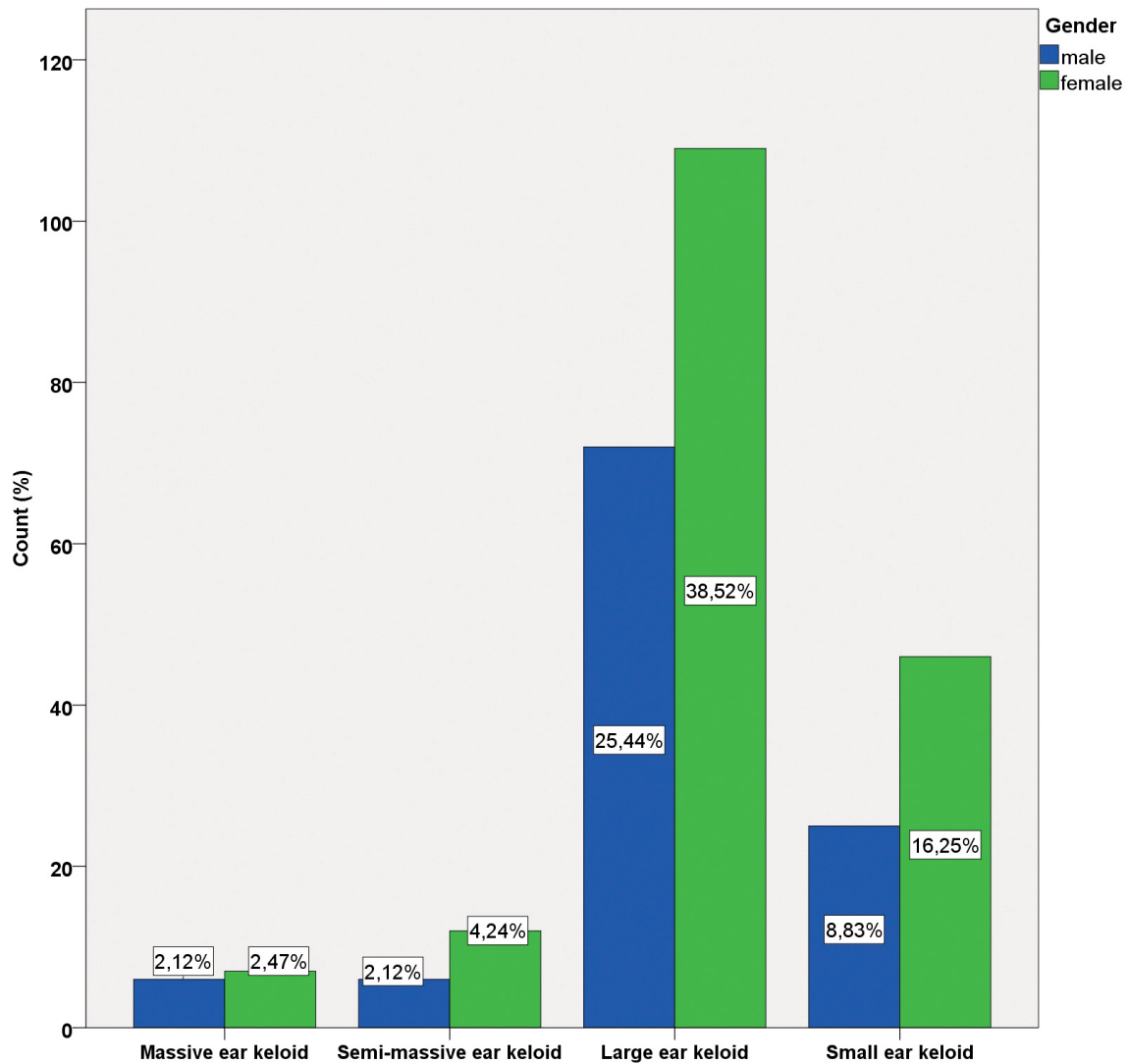
Furthermore, African/African American race was noted to be a major risk factor for development of massive and semi-massive ear keloids. The proportional difference between the two racial groups is statistically significant and shown in [Table 4](#) (95% CI of observed proportion for African American race is 66.34%-94.62%,  $Z=3.786$ ,  $P=0.0002$ ).

Prior keloid removal surgery was the most important risk factor among all patients with massive and semi-massive ear keloids. Without exception, all these patients had undergone anywhere between one to seven prior keloid removal surgeries. Prior keloid removal surgery was also the most important risk factor among patients with large ear keloids. [Table 5](#) shows the proportion of patients having undergone ear keloid removal surgery in each of these three study groups.

**Table 1. Patient characteristics.**

Patients N=	283
<b>Asians/Caucasians</b>	<b>82 (29%)</b>
Male	30
Female	52
<b>African Americans</b>	<b>201 (71%)</b>
Male	79
Female	122
<b>Massive ear keloids</b>	<b>13 (4.6%)</b>
Gender	
Male	6
Female	7
Race	
Caucasian - Asian	3
African American	10
<b>Semi-massive ear keloids</b>	<b>18 (6.4%)</b>
Gender	
Male	6
Female	12
Race	
Caucasian - Asian	2
African American	16
<b>Large ear keloids</b>	<b>181 (64%)</b>
Gender	
Male	72
Female	109
Race	
Caucasian - Asian	49
African American	132
<b>Small ear keloids</b>	<b>71 (25%)</b>
Gender	
Male	25
Female	46
Race	
Caucasian - Asian	28
African American	43

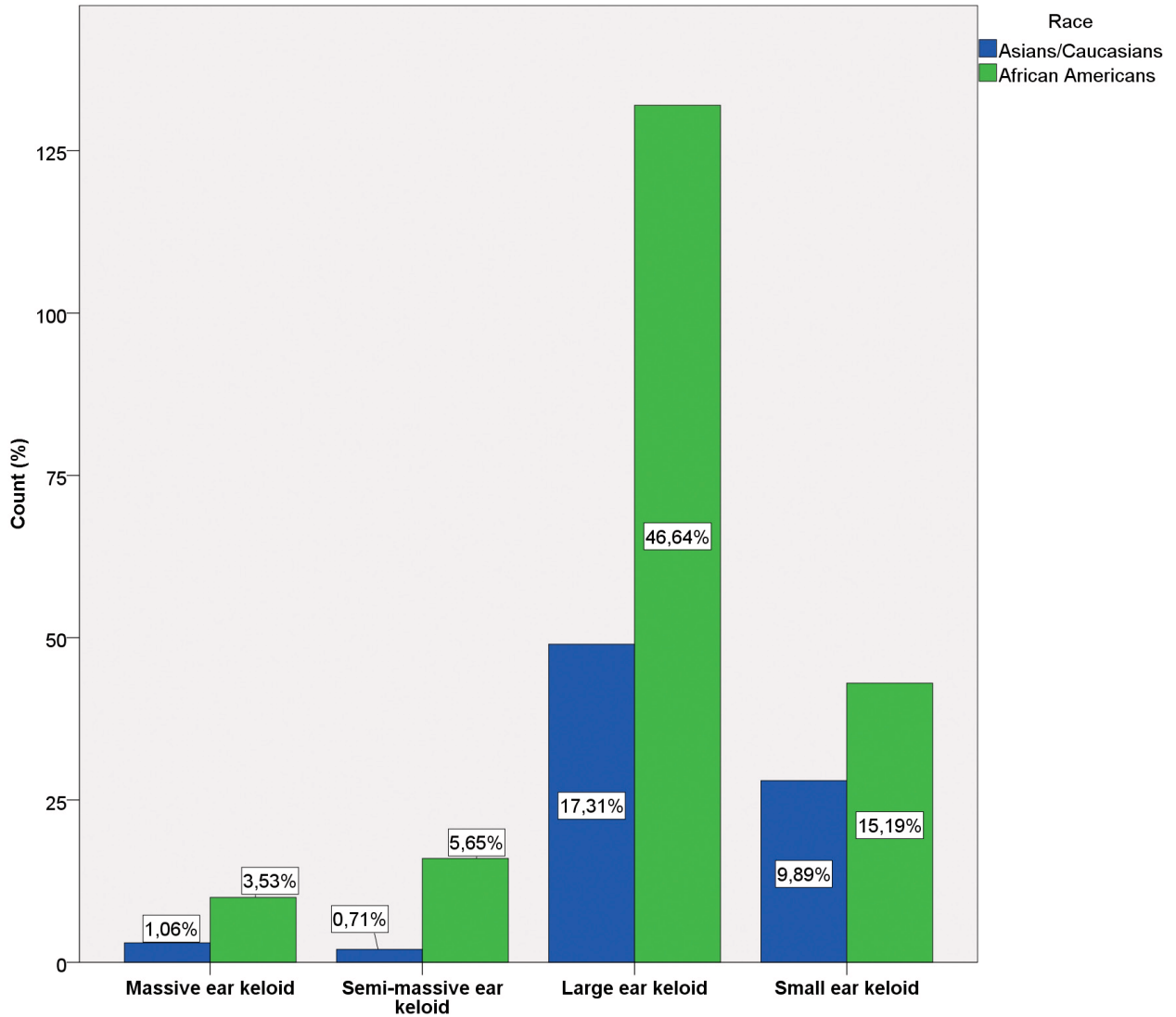




**Figure 6.** Proportion of keloid patients in each study group according to gender.

**Table 2.** Stage grouping for patients with solitary ear keloids.

Massive ear keloid	Stage 1C	Presence of only one keloidal lesion that measures greater than 10 centimeters in any dimension.
Large and Semi-massive ear keloids	Stage 1B	Presence of only one keloidal lesion that measures 2.1 – 10 centimeters in any dimension.
Small ear keloids	Stage 1A	Presence of only one keloidal lesion that measures no greater than 2 centimeters in any dimension.



**Figure 7.** Proportion of keloid patients in each study group according to race.

**Table 3.** Proportion of females v. males among all study subjects.

Gender	N	Observed proportion	95% CI of observed proportion	Test proportion	Z-statistics	P (2-sided)
Female	174	61%	55.05%–66.72%	0.5	3.701	0.0002
Male	109	39%				
Total	283	100%				

**Table 4.** Proportion of patients with massive and semi-massive ear keloids according to their race.

Race	N	Observed proportion	95% CI of observed proportion	Test proportion	Z-statistics	P (2-sided)
African American	26	84%	66.34%–94.62%	0.5	3.786	0.0002
Caucasian-Asian	5	16%				
Total	31	100%				

**Table 5. History of prior ear keloid removal surgery.**

Massive Ear Keloids						
	N	Proportions	95% CI	Test proportion	Z-statistics	P (2-Sided)
Surgery	13	100%	75.29%–100.00%	0.5	3.606	0.0003
No Surgery	0	0.00%				
Total	13	100%				
Semi-Massive Ear Keloids						
	N	Proportions	95% CI	Test proportion	Z-statistics	P (2-Sided)
Surgery	18	100%	81.47%–100.00%	0.5	4.243	<0.0001
No Surgery	0	0.00%				
Total	18	100%				
Large Ear Keloids						
	N	Proportions	95% CI	Test proportion	Z-statistics	P (2-Sided)
Surgery	131	72%	64.86%–78.41%	0.5	5.920	<0.0001
No Surgery	50	28%				
Total	181	100%				

## Discussion

Surgery is a commonly practiced therapeutic intervention for removal of ear keloids. Based on the findings of this study, the author proposes the following designations for keloid lesions.

### Primary ear keloids

A primary ear keloid is a keloid that has not been previously treated with surgery. Keloid lesions can form in any part of the ear; however, the location of the keloid solely depends on the site of the prior injury or ear piercing. All primary ear keloids start as a small skin lesion and grow over time. The longer a keloid is present, the larger it will become. [Figure 5](#) depicts several examples of primary keloids in various stages of development.

### Secondary ear keloids

A secondary ear keloid is a new keloid that forms at the site of surgery for the removal of a primary keloid. [Figure 2](#), [Figure 3](#), and [Figure 4](#) depict numerous cases of secondary ear keloids.

It is undisputable that the extent of the injury from the surgical removal of a primary ear keloid is significantly greater than the injury sustained from ear piercing. It is also logical to conclude that the extent of skin injury has a direct and linear relationship with the size and mass of keloid lesions. These two simple facts explain why keloid removal surgery can trigger development of larger keloids. Cognizant of the fact that there are patients whose keloids do not recur after surgery, we must be well aware, and acknowledge the deleterious effects of surgery, and the nightmare that is imposed on patients who end up developing large, semi-massive or massive ear keloids.

Tanaydin *et al.* reported their data on utilization of pressure devices<sup>6</sup> as adjuvant treatment after surgical excision of ear keloids, concluding that “keloid scars did not recur in 70.5% of treated patients”. This success rate, however, corresponds to a recurrence rate of 29.5%, almost one in three patients.

Recently-advocated approach of surgery in combination with adjuvant radiation therapy<sup>7,9</sup>, although it may yield to a lower keloid recurrence rate, it is by no means curative and still results in recurrence of keloids. It also exposes all patients to potentially grave adverse effects of radiation therapy.

Shin *et al.*, conducted a meta-analysis of the published data on adjuvant post-operative intra-lesional triamcinolone and radiation therapy after surgical excision of ear keloids and concluded that recurrence rates of 15.4% with adjuvant triamcinolone and 14.0% with adjuvant radiation therapy<sup>8</sup>. These recurrence rates correspond to treatment failure in almost one in six or seven patients. Massive and semi-massive keloids occur in these exact subsets of patients who fail to respond to the best surgical efforts.

Indiscriminate and repeated surgical attempts to remove ear keloids are also associated with disfigurement of the ear. By attempting to remove the entire keloid, surgeons remove part of the earlobe or performs a wedge resection and remove some of the ear cartilage and soft tissue adjacent to the keloid. Even if this approach does not lead to the recurrence of the keloid, which it often does, it will result in the loss of normal ear anatomy and a poor aesthetic outcome. [Figure 8](#) depicts several examples of such poor outcomes. A very common shortcoming of several publications on the





**Figure 8. Poor surgical outcomes for which the true incidence remains unreported.** Notice the disfiguration of normal ear anatomy and the loss of ear tissue from prior surgeries.

surgical treatment of ear keloids<sup>2-5</sup> is lack of reporting of the aesthetic outcomes.

The psychological stress and anxiety that is imposed on a young person by having to live with a worsened ear keloid is very real and life changing<sup>10</sup>. Those of us who take on the task of treating keloid patients, often teenagers and young adults, need to be very cognizant about the risks associated with the treatments that we offer to our patients. Although surgery provides a quick-fix solution to an ear keloid, exposing children and young adults to a procedure that has even 1% risk of causing massive or semi-massive ear keloid is unacceptable, let alone a 11% risk that is observed among 283 consecutive cases presented here. It is unfortunate that the data on incidence of massive or semi-massive ear keloids has never been published, but a rate of 11% among author's patients is very disturbing and resonates like a loud siren calling for more careful analysis of outcome data of all surgical interventions.

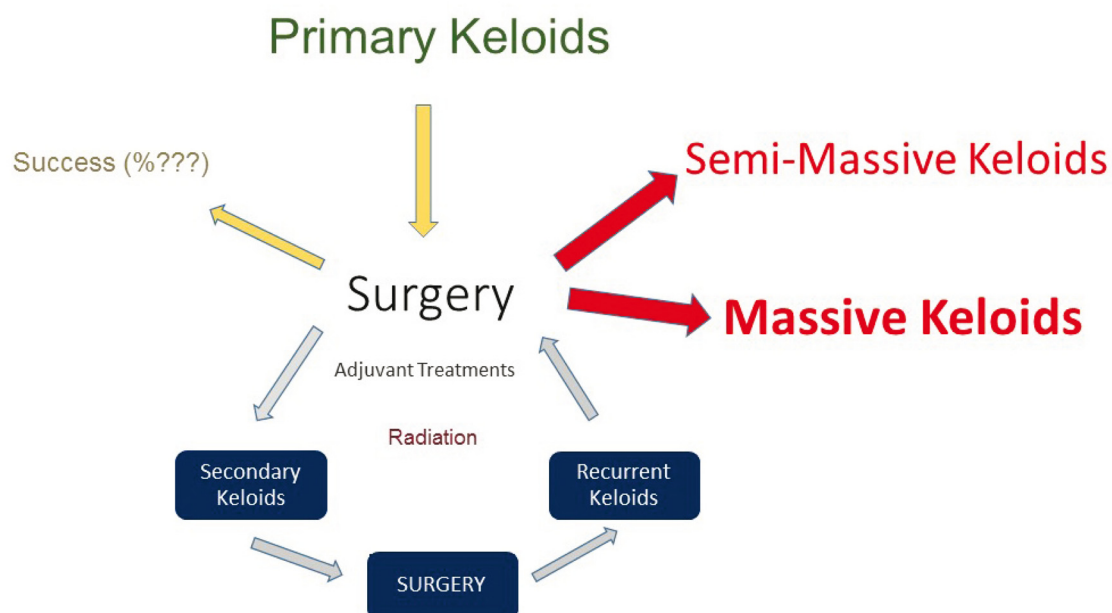
Furthermore, the carcinogenic risk of radiation therapy is real and should not be under-estimated. Let us not forget the fact that practice of radiation therapy for treatment of acne vulgaris was abandoned several decades ago, with some dermatologists referring to usage of radiation for treatment of benign skin conditions as "criminal"<sup>11</sup>. Exposing teenagers and young adults to such a treatment, even with a small long term risk, is simply unacceptable. We need to bear in mind that we are not treating elderly cancer patients with radiation; we are treating teenagers and young adults. No matter how well the ear tissue is isolated and shielded, many thousands of hematopoietic stem cells that circulate in the capillaries and venules of the ear tissue will be exposed to ionizing irradiation. The author doubts that even one radiation therapist will be willing to expose his or her own ear tissue or

that of his or her child to the radiation that is so casually offered to many young adults with KD.

Moreover, the real rate of keloid non-recurrence after adjuvant radiation therapy remains unknown. Most studies report their outcome after a short interval of few months to two years. A recent comprehensive review of adjuvant radiation therapy<sup>12</sup> for treatment of keloid lesions screened 207 publications, many of which were excluded for not describing a minimum length of follow up. The authors limited their study to 33 articles with only 10 studies providing incidence of recurrence. The mean time to recurrence was  $14.8 \pm 6.7$  months with a range of 2–36 months post-treatment. True long term recurrence rate of keloids after adjuvant radiation therapy remains unknown. Author is currently treating a patient with massive left ear keloid who had her first recurrence 13 years after receiving adjuvant radiation therapy. **Figure 2** depicts several cases of massive ear keloids in patients who had previously received adjuvant radiation therapy after surgical removal of their ear keloids.

### Need for a paradigm shift in treating primary ear keloids

The successful treatment of human diseases is reliant on thorough understanding of the underlying processes that lead to the development of particular illnesses. The basic principal of treating keloidal lesions is the destruction of the abnormal tissue with a method that will not trigger the underlying keloidal wound healing response. Surgical removal of keloids will indeed trigger this pathological wound healing response and can result in development of a much larger ear keloids. **Figure 9** depicts the vicious cycle of surgery that can results in formation of semi-massive and massive ear keloids; a cycle that all 31 patients in this study, and all those shown in **Figure 2** and **Figure 3** have been through.



**Figure 9.** Vicious cycle of keloid removal surgery that results in the formation of semi-massive and massive in ear keloids.





**Figure 10.** Successful keloid removal with contact cryotherapy for small primary and secondary (left column, bottom two cases) keloids. Notice the very minimal scarring at the site of cryotherapy. Most of these patients have enjoyed very durable and persistent results.

The development of all secondary keloids can be effectively prevented if we simply stop performing surgery on keloid patients all together. In the author's opinion, supported by his own experience, the paradigm shifting treatment approach is a move to utilize contact cryotherapy for treatment of all primary ear keloids. Furthermore, the author believes that proper application of cryotherapy can effectively remove all primary ear keloids and prevent development of all secondary keloids. Results with high therapeutic success rate have been previously reported by others<sup>13-16</sup>. **Figure 10** depicts several examples of durable results achieved by the author for patients with primary ear keloids.

Cryotherapy should be delivered properly and repeated as many times as needed. Liquid nitrogen is best applied to the keloid tissue using a properly sized hand-held applicator; such as a large cotton swab. The process should be repeated until the entire mass of keloid is frozen to the level of normal ear tissue. Within a few hours, the treated tissue becomes edematous and swollen and often forms a blister which frequently bursts and oozes serous fluid for several days. During this time frame, the treated keloid should be attended to as an open wound; thus, it is best covered with gauze and a loose dressing. Within the next several days, the treated tissue will become dehydrated and form a black-colored scab, which will remain in place for a few weeks. The scab will then gradually slough off. This process takes two to three weeks for very small keloids and up to six to eight weeks for larger keloids. In the author's experience, upon recovery from the first treatment, most keloids show 30–60% reduction in their mass. Cryotherapy should be repeated, often every four to eight weeks in the same fashion until the keloid mass is totally destroyed. Depending on the size of the primary keloid, this process takes four to eight months and results in total removal of the primary keloids in almost every patient. Pressure devices or intra-lesional steroids should be used in all patients who continue to have a keloid remnant within their ear tissue.

Pain control is critical during the application of cryotherapy as well as during the first 24 hours after treatment. Inadequate pain control will result in a lack of compliance and poor treatment outcome. All patients should be educated about the process, and prescribed proper pain control medications.

Furthermore, there is no need to perforate the body of keloid with a very large bore metallic cannula, and to run liquid nitrogen through the core of keloid<sup>17</sup>. There exist no data, and no evidence to support superiority of this invasive technique to standard, non-invasive contact cryotherapy.

Although we can successfully debulk and remove almost all primary ear keloids with cryotherapy, there is a clear need for follow up in all patients in order to detect and treat early recurrences. Repeat cryotherapy, intra-lesional steroid and/or intra-lesional chemotherapy should be considered in treating keloid recurrence.

Performing surgery to remove primary ear keloids is inherently contrary to both of the above principles. Surgery, by its nature,

induces new injury to the skin, and as shown in **Figure 8**, the surgical removal of a primary keloid frequently results in the loss of surrounding normal ear tissue. The loss of normal ear tissue, even in the absence of future keloid recurrence, will often result in an unacceptable aesthetic outcome. The worsening of ear keloids after surgical excision is caused by the triggering of the same dysregulated wound healing response, yet to a new dermal injury that is more extensive in nature than the injury from the ear piercing itself.

There are many circumstances – but most importantly when surgery is performed on a patient – that we have the duty to obtain “informed consent” and not just a “permission to operate”. Simple disclosure of the general risks associated with a surgical procedure is clearly inadequate. It is our professional duty to advise all keloid patients of the specific risks that are associated with the surgical removal of their keloids. We are obligated to disclose the risk of developing massive and semi-massive keloids to each and every patient who is advised to undergo surgery. Through the informed consent process, we have the ethical and moral obligation of showing the images of massive and semi-massive ear keloids to our patients, and informing them that with keloid surgery, there is a risk of developing such life-changing complications. We are also obligated to discuss alternative procedures, or conservative nonsurgical approaches. As healers who are licensed to practice medicine, we have the obligation of respecting clinical data, disease biology and the process of informed consent, all of which translate into improvement in: treatment outcomes for our patients.

## Conclusions

Although this study is limited by its size, and patients were drawn from only one medical practice that does not offer surgery for treatment of keloids, several interesting factors stand out as risk factors for development of large, semi-massive and massive ear keloids.

- Prior keloid removal surgery was the most important risk factor for development of massive and semi-massive ear keloids. Without exception, all these patients had undergone anywhere between one to seven prior keloid removal surgeries.
- Prior keloid removal surgery was the most important risk factor for development of large ear keloids with 72% of patients having prior keloid removal surgery.
- African/African American race was noted to be a major potential risk factor in all four groups, most importantly among those with massive, semi-massive ear keloids, with only five Caucasians/Asians among the 31 patients (11%) in both these groups.

## Recommendations

The goal of treatment for keloid lesions, and ear keloids in particular, should not only focus on removal of the keloid tissue, but most importantly on two other very important principles:

1. Prevention of damage to the ear tissue

## 2. Prevention of the recurrence of the keloid

Topical contact cryotherapy should be the primary mode of treatment for all primary and secondary ear keloids. This approach will prevent the development of incurable secondary and, large, semi-massive and massive keloids and eliminate the need for hazardous adjuvant radiation therapy.

### Data availability

All raw data relevant to the study are provided in tables above.

### Competing interests

No competing interests were disclosed.

### Grant information

The author(s) declared that no grants were involved in supporting this work.

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# Open Peer Review

Current Referee Status:



Version 2

Referee Report 05 May 2017

doi:10.5256/f1000research.11970.r22098



**Mohamed B.H.T. Abdel-Naser**

Department of Dermatology, Andrology and STIs, Faculty of Medicine, Ain Shams University, Cairo, Egypt

This is a retrospective study in which the author examined the demography of keloid patients. The following points need consideration.

1. The manuscript is too long and it can be markedly reduced without any impact on the quality of the study. For example
  - a. Fig. 1. No need for this figure in the present study and it can be omitted together with its relevant text. Both can be useful for a separate review article.
  - b. In the results section, patients data are given in the text and repeated in table. 1. This is unnecessary repetition. In general, what is mentioned in text should not be mentioned in table and vice versa. In fact, author can insert all patients' data in a single table.
  - c. Table 2. Author gave a short account of another staging system of keloid which i believe more reliable (as it is objective) than the subjective visual method of the present study. However, what is the rational of mentioning this method and table 2 in this study? Both can be omitted.
  - d. Tables 3 and 4 can be easily incorporated in a single table without many details, such as p values. Significance can be marked with asterisk (e.g., for gender), dagger (e.g. for race), etc as a footnote. In fact both can be incorporated in table 1.
  - e. Figures 6 and 7 can be combined in one figure and the significant columns labelled (with asterisk, dagger etc) and amended as a footnote.
2. The aim of the study is not clear and perhaps should be added in a clear statement (s).
3. The author suggested that age of patients and duration of keloid are important factors, but the study lacks any correlation with these 2 parameters.
4. The discussion section is not focusing on the results of this retrospective study. Is there any reason (s) apart from genetics to explain the significant tendency of Africans to develop keloids? Are fibroblasts of Africans different from Caucasians? Is there any additional explanation(s), apart from ear piercing, for the gender difference in keloid formation? The author is not in favor of surgical removal of keloids because of the risk of recurrence and massive keloid formation. Is this risk solely related to surgical injury? Does the skill of the surgeon play a role? Does the suture material or postoperative wound infection contribute to this unfavorable outcome? In general there are several confounding factors that need to be discussed instead of elaborating on other methods not related to this retrospective study.

5. The mentioned recommendations are not appropriate in this study. Author can work on separate review article to discuss in details the different therapeutic modalities of keloids and the pros and cons of each method. In the retrospective study, the author is expected to discuss his findings.

**Is the background of the cases' history and progression described in sufficient detail?**

Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

No

**Is the conclusion balanced and justified on the basis of the findings?**

No

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Referee Report 06 April 2017

doi:10.5256/f1000research.11970.r21592



**Robert Sidbury**

Seattle Children's Hospital, University of Washington School of Medicine , Seattle, WA, USA

I appreciate Dr Tirgan's replies. I certainly endorse his overarching messages that injury to the skin is a major predisposing factor to keloid development, and surgery is certainly a form of injury to the skin. I also wholeheartedly endorse the need for a full discussion with affected patients about the full range of treatment options, both medical and surgical, and the risks and benefits of both. I continue to feel that while cryotherapy is indeed an option, and clearly a successful one in many cases, it is not viable for all and in some cases surgery can be the best choice with the aforementioned caveats. As for the lack of a billing code for cryotherapy as a possible reason for this not being offered to patients, I guess I can't speak for all who practice in this realm but only myself: I don't ever personally operate on keloids nor have any financial connection to those who do so my own motivation is not so conflicted. I can and do bill for cryotherapy, keloids, warts or other, when appropriate. All of that said, this is a very nice review of the topic and will no doubt be useful to providers (and patients) as they consider their options.

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**



Referee Report 31 March 2017

doi:10.5256/f1000research.11970.r21414



**Amy J. McMichael**

Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, NC, USA

I reviewed the revision of the Tirgan article and it appears much more clearly organized. Results are in the results section. The discussion points are based upon actual data. The manuscript is quite long, but the slides are great.

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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### Version 1

Referee Report 09 January 2017

doi:10.5256/f1000research.10237.r19062



**Amy J. McMichael**

Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, NC, USA

This is a good accounting of keloids with many cases for discussion. The placement of new data in the discussion section is a bit off-putting for the reader. I would recommend placing all the charts in the Results section rather than having them in the Methods Section. Also, there needs to be more than just the grouping of keloids as presented. Basically, this is a list of keloids. There needs to be some correlation drawn or statistics to note associations rather than just descriptive stats. This is a great start, but just needs more to really give the reader information that is useful. I recommend not putting new data in the discussion and conclusion and moving this to the results.

The analysis used on the cases should be included in the methods section. The discussion should focus on the natural history of all the things that are discussed in the results sections.

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Referee Report 15 November 2016

doi:10.5256/f1000research.10237.r17447



- **Robert Sidbury**

Seattle Children's Hospital, University of Washington School of Medicine , Seattle, WA, USA

Overall this is a nice review. There are certain small additions I would make (e.g. a line somewhere capturing the idea that keloids can be seen in certain syndromes disproportionately such as Rubinstein-Taybi syndrome). This might reasonably be placed in the abstract (e.g. KD is an inherited wound healing ailment, frequently seen among Africans/African Americans, Asians, and in some genetic disorders such as Rubinstein Taybi syndrome). A notation like this in the introduction would also make more complete.

The aforementioned criticism pales in comparison with my overarching concern that this article has more of an agenda than just information dissemination. The agenda is that surgery is bad for ear keloids and the author does not shy away from this opinion. My concern is not that he expresses this opinion, even advocates for it to a certain extent if he believes it to be true, but the lengths he takes this, and the way he uses his "data" asymmetrically to make this point gives me pause.

First, what about the point itself? Is it valid? Is surgery bad for keloids? Yes, surgery is an injury to the skin which can itself promote keloid formation, indeed so much so that our surgeons will not operate to remove or debulk keloids in certain areas (eg neck, trunk). However, they do believe and I have shared plenty of patients to validate that ear keloids can be effectively removed in a sustainable, cosmetically acceptable way without necessarily (and in fact rarely) resorting to radiation therapy adjunctively. This sort of response is well-documented in the literature they just don't happen to be references this author cites:

- Triamcinolone after surgery as effective as radiation therapy (and both can be effective) at preventing recurrence <sup>1</sup>
- Pressure clips after surgery can prevent recurrence (this is technique used by my colleagues in Plastic Surgery to good effect) <sup>2</sup>

There are countless other references of success using surgery with acceptable risk-benefit profiles.

Second, where do I believe the author goes beyond simply stating his opinion, backed up by his data, that surgery can lead to recurrence and poor outcome?

- First paragraph page 3, final sentence, "...unfortunately, ear keloids will continue...". This is stated as if it is ALWAYS the case and it simply is not.
- Why did he not include post-otoplasty patients in study?
- p 8 Results: Don't have experience with their own surgical successes because none of these patients have that modality ("do not offer surgery for treatment of keloids"). Therefore the only patients they see are surgical failures.
- p 8 under Secondary Ear Keloids: "Cognizant of the fact that there are patients whose keloids do not recur after surgery..." and then there is no balance in what follows. This context that author describes speaks to the need for an appropriate and careful risk-benefit discussion but not necessarily not offering surgery at all when there are many reasons why it is sometimes the right choice. What if the keloid itself is life altering? What if they do not have time to return for repeated liquid nitrogen over the course of a year? With the attendant blistering and healing phases played out with each treatment? And the cost?

- p 10 paragraph 2: "1% risk of causing massive or semi-massive ear keloids is unacceptable" all depends on patient and context.
- Figure 6: "after" shots should be paired with "before" shots; I can imagine at least some of these outcomes potentially preferable to keloid it replaced but can't know without seeing images.
- p 10: Need for a paradigm paragraph # 1. Stop all surgery, cryo for all...this just isn't practical or medically justifiable.
- p 10 cryotherapy paragraph: This just isn't possible for all patients. Problems include time, \$, quality of life during treatment, incomplete response because not all patients respond to cryo; post inflammatory pigment alteration secondary to cryo especially in darker skinned patients which this author does not mention at all.

So, in summary, this is simply too one-sided and agenda driven to be an appropriate publication in my opinion. Could it be modified? Sure. Present cryotherapy and other options alongside surgery and feel free to opine but a more balanced presentation with updated references would be required for me to endorse.

## References

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**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 18 Nov 2016

**Michael Tirgan**, Keloid Research Foundation, USA

Dear Dr. Sidsbury:

Thank you very much for taking the time to review and comment on my publication. Peer review plays an important role in publishing research material. I truly appreciate your detailed and thorough review and each and every comment you have made. I hereby address the points you have raised.

1. As for referencing to Rubinstein-Taybi Syndrome - This manuscript is focused on providing data about Massive Ear Keloids. It is by no means review of the disorder.
2. As for your comment about my point being that "surgery is bad for ear keloids" – I am personally convinced that to be the case. Keloid is a genetic disorder that involves much of the normal appearing skin. It is not limited to the area of a keloid growth, therefore surgery cannot cure it. There are numerous publications that have eloquently explained this

fact. This conclusion is backed by data as presented in the manuscript. It is also backed by clinical observation of some physicians, and parents and relatives of keloid patients, who dissuade patients from undergoing surgery.

3. As for your comment “therefore the only patients they see are surgical failures” - this is simply not correct. Patients shown in Figure 5 are some of my patients who presented with very early stages of ear keloid and had chosen a non-surgical approach. As for breakdown of the study cohorts, there were 283 patients in the study. 31 patients had massive or semi-massive ear keloids. Among 181 patients with large keloids, only 73% had prior surgery and 27% rest of these patients never had surgery. Of the 71 patients in the “small ear keloid” majority had not undergone surgery. Altogether, more than a third of all patients did not have surgery.
4. As for your comment about this manuscript being “agenda driven” - I simply disagree with you. My conclusions are rather data driven. We - as physicians and as healers – have the ethical and moral obligation of providing our patients with the best available treatment. The Declaration of Geneva of the World Medical Association binds us with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients.

The Declaration of Geneva also states that “The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency and accessibility.” Purpose of this study was to exactly do what the Declaration of Geneva was intended us to do. Data provided in the manuscript points to the shortcomings of surgery by way of causing massive and semi-massive keloids. Manuscript provides argument as to why this may be the case. All conclusions are driven by data.

5. As for your comments about surgery that “This sort of response is well-documented in the literature they just don't happen to be references this author cites”, I would refer to the two references provided at the conclusion of your comments.

Shin et. al reported “The recurrence rate after surgical excision of an ear keloid in the triamcinolone group was estimated as 15.4 percent. The recurrence rate in the radiation therapy group was estimated as 14.0 percent.”

Tanaydin et. al reported “Keloid scars did not recur in 70.5% of treated patients”. By doing the math, the recurrence rate was 29.5% among patients who used custom made pressure clips after surgery.

There is no doubt that some patients develop massive and semi-massive keloids - the ones who fail to respond to the best surgical efforts - i.e. the 14-15% (one in six patients) reported by Shin and 29.5% (one in three) reported by Tanaydin.

I hope to see more publications about the incidence of massive and semi-massive ear

keloids. As of this date, searching pubmed does not locate even one publication about incidence of massive ear keloids.

I do advocate cryotherapy as primary treatment of all bulky ear keloids. There are several references that lend support to the usage of cryotherapy for treatment of ear keloids. Cryotherapy, as a treatment modality for keloids is also mentioned in every textbook of dermatology and in every overview of keloids, however, hardly any dermatologist or plastic surgeon uses it. I wonder why? I know for fact that there are no billing codes for application of cryotherapy for treating keloids.

6. As for “not including post-otoplasty cases” – there were only 14 patients. I have written is separate manuscript about this cohort.
7. As for figure 6 – the point was to show less than ideal aesthetic outcome of ear keloid surgery.
8. As for paradigm shift to stop surgery – I think it can be done. Although surgery is a quick-fix and results in immediate removal of ear keloids, it does cause long term harm to many patients. To this date, we do not have a methodology to identify who will be the next patient at risk of developing a massive ear keloid after surgical removal of a small primary ear keloid. In my data set, the rate is close to 11%. To know the exact risks and outcomes, we need establish a Keloid Surgery Registry, and register each and every keloid patient who undergoes surgery, and follow them for several years. In absence of such data, or data from a well-designed randomized trial, all we can do is to inform our patients of the potential risks of keloid surgery.

There are many circumstances – but most importantly when surgery is performed on a patient – that we have the duty to obtain “informed consent” and not just a “permission to operate”. We also have the duty to advise our patients of the specific risks of the procedure. We do know that disclosure of the general risks that are associated with any surgical procedure is not adequate. We are obligated to disclose the risk of developing massive and semi-massive keloids to each and every patient who is to undergo keloid removal surgery. We are also obligated to discuss alternative procedures, or conservative nonsurgical approaches with our patients. Through informed consent process, we have the ethical and moral obligation of showing the images of massive and semi-massive ear keloid to their patients, and informing them that with keloid surgery, there is a risk of developing such life-changing complications.

9. As for the cost, risks, rate of skin discoloration and other aspects of cryotherapy, only a well-designed randomized study to compare surgery to contact cryotherapy will be able to answer all these valid points. I hope that there will be enough interest to support and fund such a study.
10. Finally, I am of the view that we all should respect data, disease biology and the process of informed consent. I only wish to improve the outcome of our patients. I hope that through collaborations with physicians like yourself, we can join forces and tackle this very hard-to-treat disorder.



Thank you again for all your comments.

Michael H. Tirgan, MD

***Competing Interests:*** No competing interests were disclosed.

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